CLINICAL AND IMAGING ASSESSMENT OF ACUTE COMBAT MILD TRAUMATIC BRAIN INJURY IN AFGHANISTAN

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SUPPLEMENTAL INFORMATION

Supplemental Methods

All mTBI participants had a Glasgow Coma Scale of 15 at the time of consent and were interviewed and examined by the research staff (JD, DR, TM, OA), who also reviewed available field medical records. Control or mTBI participants were excluded if they had a lifetime history of severe TBI or conditions that are known to or could reasonably be expected to alter DTI signal characteristics, including cerebrovascular disease, multiple sclerosis, hypoxic/ischemic brain injury, HIV, severe electrolyte disturbance, liver failure, renal failure, heart failure, alcohol abuse or longstanding psychiatric disease. Additional inclusion criteria for both groups were willingness to participate in the study, ability to communicate and comply with the study protocol and ability to provide consent. Both mTBI and control subjects were excluded if they had contraindications to MRI, such as claustrophobia, retained metallic foreign objects or inability to lie still in a supine position for the duration of the scan. The inclusion criteria were based on the mTBI/concussion as defined by the American Congress of Rehabilitation Medicine. All mTBI participants also satisfied the Department of Defense definition of mTBI/concussion (DTM 09-033)[1]. No participant was excluded because of incongruences between the American Congress of Rehabilitation Medicine and the DoD mTBI/concussion definitions.

RPCSQ[2] is a self-administered questionnaire assessing 16 common post-concussive symptoms on a scale of 0 (none) to 4 (severe) covering three domains: cognitive (“forgetfulness, poor memory”, “poor concentration”, “taking longer to think”), emotional (“being irritable, easily angered”, “feeling depressed or tearful”, “feeling frustrated or inpatient”) and somatic (“headache”, “feeling of dizziness”, “nausea and/or vomiting”, “noise sensitivity, easily upset by loud noise”, which many patients also equate to tinnitus, “sleep disturbance”, “fatigue, tiring

more easily", "blurred vision", "light sensitivity, easily upset by bright light", "double vision", "restlessness").

The PCLM[3] is a 17 item self-administered questionnaire tying symptom ratings to events experienced during military service, using a scale of 1 (not at all) to 5 (extremely).

The BDI[4, 5] is a self-administered 21 item questionnaire corresponding to symptoms of depression rated on a severity scale of 0 (no symptoms) to 3 (severe symptoms).

The Combat Exposures Scale[6] (CES) measures the self-reported frequency of selected wartime dangerous situations such as combat patrols, being under enemy fire, being surrounded by the enemy, number of soldiers killed in action (KIA) or missing in action (MIA) in one's unit, firing rounds at the enemy, witnessing someone hit by incoming or outgoing rounds and being in danger of being killed or injured. The CES measures each of the 7 items using a 5 point scale (1 is "no", 2 is "1 to 3 times", 3 is "4 to 12 times", 4 is "13 to 50 times", and 5 is "51+ times"). Each item is weighted differently based on the severity of the experience, the total scores ranging from 0−41.

The neurological examination consisted of cranial nerve, motor, sensory, coordination, deep tendon reflex, posture and gait assessments.

The ANAM[7] is sanctioned by the Department of Defense for baseline neurocognitive assessment in all deploying troops. It is also available in deployed setting. The ANAM includes a collection of cognitive modules. The first (SRT) and repeat (2SRT) simple reaction time for basic neural processing are expressed in milliseconds, lower scores indicating a faster reaction time. The code substitution – learning (CSL) for associative learning, procedural reaction time (PRT) for processing speed, mathematical processing (MTP) for working memory, matching to

sample (MTS) for visual spatial memory and code substitution – delayed (CSD) for delayed memory are expressed as throughput, which is derived from percent correct answers divided by mean reaction time, reflecting performance across both dependent variables. Higher scores indicate better performance. Throughput has been shown to have greater sensitivity and reduced variability compared to reaction time or accuracy alone[8]. The cognitive modules are preceded by a sleepiness and general level of alertness scale, a self-rated one to seven score, one representing the maximum level of alertness. Post-injury cognitive performance group comparisons were measured relative to pre-deployment baselines rather than comparing absolute ANAM scores. Using individual baseline neurocognitive scores minimizes potential false-positive errors[9].

The TOMM is a clinician administered tool of effort to discern malingerers from bona fide cognitively impaired individuals[10]. The testing paradigm involved a single TOMM trial for subjects with a score higher or equal to 45 and a second trial for subjects with a first TOMM score lower than 45.

The BESS[11] is a clinician administered balance test which includes single, double and tandem stance assessment on firm and foam (unstable) surfaces, each held for 20 seconds, with the participant's hands on the hips and eyes closed. The score is a representation of cumulative errors.

Data regarding immediate effects of injury were collected as follows: loss of consciousness was scored as none, <5 minutes, 6-15 minutes, or 16-30 minutes. No subject reported loss of consciousness >15 minutes. Alteration of consciousness was scored as none, <5 minutes, 6-59 minutes, or 1-24 hours. No subject reported alteration of consciousness greater

than 24 hours. Anterograde and retrograde amnesia were scored separately as none, <5 minutes, 6-59 minutes, or 1-24 hours. No subject reported amnesia of either type greater than 24 hours.

The specific acquisition DTI parameters were set to accommodate limitations on patient scanning time and imaging data file size, taking into account the available infrastructure and the logistics of transferring such large data files from Afghanistan to the United States. Unique sources of artifact represented by the effects of wind gusts and vibration from high speed aircraft take off on the MRI machines located in trailers on the combat hospital compounds further restricted scan duration. The geographical distance between the acquisition and analysis study sites posed challenges for the quick feedback needed on each individual scan quality. It required considerable coordination efforts between the five relay server sites involved in the imaging data file transfer across 12 time zones. One server site (Germany) required manually operated data file transfers as part of the interacting interface between the Department of Defense (DoD) and a civilian institution. Nonetheless, processing and analysis was completed within 24 hours of acquisition in all cases.

Recovery time, defined as days from injury to final disposition (e.g. return to duty), was used as a surrogate for outcome. Service members who sustained a blast-related mTBI were prescribed rest and symptomatic treatment until they became asymptomatic at rest and during a final exertion test. Treatment and return to duty decision making was conducted by the clinicians involved in patient care and followed a standardized algorithm based on the Department of Defense directive-type memorandum "Policy Guidance for Management of Concussion/Mild Traumatic Brain Injury in the Deployed Setting[1]. Treating clinicians were not aware of MRI results and based decisions largely on symptom resolution, independent of initial test performance.

Interpretation of conventional MRI and DTI data was performed in a blinded manner. With the exception of BESS, clinical testing was self-administering, requiring minimal interaction with the research staff beyond instructions. Although efforts were made, occasional involvement in the clinical care of mTBI participants by the research staff precluded a completely blinded administration of BESS in a consistent manner.

Power calculations were based on correlations between the primary outcome (DTI variables) and time to return to duty. These calculations assumed that a correlation of 0.5 or greater would be clinically meaningful. Considering ten or more candidate DTI abnormalities or combinations, the alpha significance level was set to 0.005 to correct for multiple comparisons by the Bonferroni method. With these assumptions, a sample size of 60 subjects to achieve a 90% likelihood of a statistically significant result was considered adequate. A 50% larger sample size (90 mTBI participants) was set to take into consideration possible non-linear relationships and non-parametric correlations. The final recruiting sample (115 mTBI subjects) took into account an estimated loss of 20% due to participant screening failure, dropout or missing data.

All participants provided written informed consent before enrolment. None of the participants received monetary compensation for participating in this study. This research was approved by the Department of Defense Central Command Medical Research and Materiel Command Institutional Review Board and complied with human research ethics regulations.

Supplementary Tables

Table e-1. Regions of interest considered for analysis of DTI Data (Numbering, nomenclature and parenthetical notes from Zhang et al., 2010[12])			
3	Superior frontal gyrus right	68	Superior frontal gyrus left
4	Middle frontal gyrus right	69	Middle frontal gyrus left
5	Inferior frontal gyrus right	70	Inferior frontal gyrus left
22	Middle fronto-orbital gyrus right	87	Middle fronto-orbital gyrus left
29	Corticospinal tract right	94	Corticospinal tract left
30	Inferior cerebellar peduncle right	95	Inferior cerebellar peduncle left
31	Medial lemniscus right	96	Medial lemniscus left
32	Superior cerebellar peduncle right	97	Superior cerebellar peduncle left
33	Cerebral peduncle right	98	Cerebral peduncle left
34	Anterior limb of internal capsule right	99	Anterior limb of internal capsule left
35	Posterior limb of internal capsule right	100	Posterior limb of internal capsule left
36	Posterior thalamic radiation (include optic radiation) right	101	Posterior thalamic radiation (include optic radiation) left
37	Anterior corona radiata right	102	Anterior corona radiata left
38	Superior corona radiata right	103	Superior corona radiata left
39	Posterior corona radiata right	104	Posterior corona radiata left
40	Cingulum (cingulate gyrus) right	105	Cingulum (cingulate gyrus) left
43	Superior longitudinal fasciculus right	108	Superior longitudinal fasciculus left
44	Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) right	109	Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) left
45	Inferior fronto-occipital fasciculus right	110	Inferior fronto-occipital fasciculus left
46	Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus) right	111	Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus) left
47	External capsule right	112	External capsule left
48	Uncinate fasciculus right	113	Uncinate fasciculus left
49	Pontine crossing tract (a part of middle cerebellar peduncle) right	114	Pontine crossing tract (a part of middle cerebellar peduncle) left
50	Middle cerebellar peduncle right	115	Middle cerebellar peduncle left
52	Genu of corpus callosum right	117	Genu of corpus callosum left
53	Body of corpus callosum right	118	Body of corpus callosum left
54	Splenium of corpus callosum right	119	Splenium of corpus callosum left
55	Retrolenticular part of internal capsule right	120	Retrolenticular part of internal capsule left

Table e-2. Enrolment site comparisons (Demographics, time from injury to MRI scan)						
	mTBI			CONTROLS		
	KAF (N=72)	LNK (N=23)	P Value	KAF (N=89)	LNK (N=12)	P Value
Age						
Median (years)	25	25	0.42[U]	28	28	0.35[U]
Range (years)	19-41	20-32		19-48	21-32	
Enlisted	67	22	1.00[F]	66	12	0.06[F]
Officer	5	1		23	0	
Male	72	21	0.06[F]	69	10	1.00[F]
Female	0	2		20	2	
Time from injury to MRI scan						
Mean±SD (days)	3.69±1.63	3.96±2.06	0.7605[U]	N/A	N/A	
Range (days)	1.0-8.0	1.0-8.0		N/A	N/A	

KAF Kandahar Air Field; LNK Camp Leatherneck;
[U] Mann Whitney U test; [F] Fisher's exact test;
mTBI mild traumatic brain injury

Table e-3. Rivermeade Post-Concussion Symptom Questionnaire (RPCSQ),

Group comparisons by individual symptoms

RPCSQ Symptom	mTBI mean±SD N=95	CTL mean±SD N=101	p Value (Mann Whitney U)	Cohen's d	Effect-size r
Headache	2.07 ± 1.03	0.27 ± 0.66	p=0.0000001	2.08	0.72
Noise sensitivity, easily upset by loud noise	1.81 ± 1.44	0.25 ± 0.74	p=0.0000001	1.41	0.58
Taking longer to think	1.56 ± 1.28	0.24 ± 0.64	p=0.0000001	1.30	0.55
Dizziness	1.06 ± 1.09	0.06 ± 0.24	p=0.0000001[F]	1.27	0.54
Fatigue, tiring more easily	1.64 ± 1.32	0.34 ± 0.78	p=0.0000001	1.20	0.51
Poor concentration	1.49 ± 1.32	0.29 ± 0.70	p=0.0000001	1.14	0.49
Sleep disturbance	1.62 ± 1.45	0.40 ± 0.92	p=0.0000001	1.00	0.45
Restlessness	1.17 ± 1.22	0.23 ± 0.66	p=0.0000001	0.99	0.44
Nausea and/or Vomiting	0.75 ± 1.00	0.05 ± 0.33	p=0.0000001[F]	0.94	0.43
Irritable, easily angered	1.28 ± 1.25	0.31 ± 0.76	p=0.0000001	0.94	0.42
Forgetfulness, poor memory	1.38 ± 1.25	0.37 ± 0.90	p=0.0000001	0.93	0.42
Light sensitivity, easily upset by bright light	1.08 ± 1.15	0.22 ± 0.70	p=0.0000001[F]	0.90	0.41
Frustrated, Impatient	1.19 ± 1.25	0.29 ± 0.70	p=0.0000001	0.89	0.41
Depressed, Tearful	0.82 ± 1.06	0.11 ± 0.44	p=0.00006[F]	0.87	0.40
Blurred vision	0.52 ± 0.94	0.07 ± 0.64	p=0.0005[F]	0.68	0.32
Double vision	0.20 ± 0.59	0.02 ± 0.20	p=0.12[F]	0.41	0.20
RPCSQ Total score	19.77 ± 12.92	3.62 ± 7.13	P=0.0000001	1.55	0.61

mTBI mild traumatic brain injury; CTL control; [F] Fisher's exact test

Table e-4. Rivermeade Post-Concussion Symptom Questionnaire (RPCSQ),
Subgroup comparisons of enlisted men only

RPCSQ Symptom	mTBI mean±SD N=87	CTL mean±SD N=65	p Value (Mann Whitney U)	Cohen's d	Effect-size r
Headache	2.08 ± 1.05	0.32 ± 0.73	p=0.000001	1.95	0.70
Noise sensitivity, easily upset by loud noise	1.85 ± 1.46	0.26 ± 0.80	p=0.0000001	1.35	0.56
Dizziness	1.10 ± 1.11	0.09 ± 0.29	p=0.0000001[F]	1.25	0.53
Taking longer to think	1.60 ± 1.26	0.32 ± 0.73	p=0.0000001	1.24	0.53
Fatigue, tiring more easily	1.69 ± 1.31	0.38 ± 0.88	p=0.0000001	1.17	0.51
Poor concentration	1.55 ± 1.32	0.40 ± 0.81	p=0.0000001	1.05	0.46
Sleep disturbance	1.68 ± 1.44	0.43 ± 1.00	p=0.0000001	1.01	0.45
Restlessness	1.20 ± 1.22	0.26 ± 0.73	p=0.0000002	0.94	0.42
Nausea and/or Vomiting	0.78 ± 1.02	0.06 ± 0.39	p=0.0000001[F]	0.93	0.42
Forgetfulness, poor memory	1.43 ± 1.24	0.4 ± 1.05	p=0.000002	0.90	0.41
Light sensitivity, easily upset by bright light	1.09 ± 1.14	0.28 ± 0.82	p=0.000002[F]	0.82	0.38
Frustrated, Impatient	1.20 ± 1.23	0.35 ± 0.78	p=0.000023	0.83	0.38
Irritable, easily angered	1.33 ± 1.25	0.40 ± 0.86	p=0.000003	0.82	0.38
Depressed, Tearful	0.76 ± 1.10	0.14 ± 0.53	p=0.000046[F]	0.72	0.34
Blurred vision	0.53 ± 0.97	0.08 ± 0.32	p=0.000444[F]	0.62	0.30
Double vision	0.21 ± 0.61	0.03 ± 0.25	p=0.03[F]	0.39	0.19
RPCSQ Total score	20.18 ± 12.80	4.28 ± 7.93	0.0000001	1.50	0.60

mTBI mild traumatic brain injury; CTL control; [F] Fisher's exact test

Table e-5. PCLM, BDI, CES and BESS
Subgroup comparisons of enlisted men only

TEST	mTBI N	CTL N	mTBI Mean ± SD	CTL Mean ± SD	P value (Mann-Whitney U)	Cohen's *d*	Effect size *r*
BESS	81	64	17.94 ± 8.34	15.42 ± 8.89	0.08[t]	0.29	0.14
BDI	87	65	7.34 ± 6.57	2.73 ± 5.12	0.000001	0.78	0.36
PCLM	87	65	32.36 ± 13.11	20.95 ± 7.01	0.000001	1.09	0.48
CES	86	65	19.08 ±9.05	6.42 ± 9.15	0.000001	1.39	0.57

[t] Student's t-test; BESS Balance Error Scoring System, BDI Beck Depression Inventory, PCLM Post-traumatic Stress Disorder Checklist Military, CES Combat Experience Scale, mTBI mild traumatic brain injury, CTL control

Table e-6. Delta ANAM (change from pre-deployment baseline to post-injury performance) ***Subgroup comparisons of enlisted men only***					
ANAM modules	mTBI (N=81) mean ± SD	CTL (N=57) mean ± SD	P values (Mann-Whitney U)	Cohen's *d*	Effect size *r*
Sleep index	0.83 ± 1.34	-0.16 ± 1.11	0.000032	0.80	0.37
Simple Reaction Time	77.19 ± 151.22	-13.26 ± 53.11	0.000003	0.80	0.37
Simple Reaction Time Repeat	95.62 ± 211.98	3.49 ± 44.29	0.000109	0.60	0.29
Procedural Reaction Time	-12.32 ± 18.87	-0.70 ± 16.70	0.000170	-0.65	-0.31
Code Substitution Learning	-4.01 ± 10.25	3.30 ± 9.71	0.000092	-0.73	-0.34
Code Substitution Delayed	-7.75 ± 16.68	3.84 ± 14.05	0.000021	-0.75	-0.35
Mathematical Processing	-3.02 ± 6.65	1.58 ± 6.44	0.000060	-0.70	-0.33
Matching to Sample	-7.17 ± 14.42	2.67 ± 9.23	0.000007	-0.81	-0.38

Table e-7. Baseline Automated Neurocognitive Assessment Metrics (ANAM)			
ANAM module	mTBI (N=87) mean±SD	CTL (N=84) mean±SD	P value (Mann Whitney U)
Sleep index	2.15 ± 1.15	1.97 ± 0.95	0.39
Simple Reaction Time	247.7 ± 20.73	257.5 ± 48.8	0.21
Simple Reaction Time Repeat	257.2 ± 32.23	260 ± 40.31	0.71
Procedural Reaction Time	103 ± 12.94	104.2 ± 13.65	0.58
Code Substitution Learning	56.21 ± 11.97	56.57 ± 10.67	0.89
Code Substitution Delayed	49.18 ± 14.17	46.14 ± 17	0.25
Mathematical Processing	21.03 ± 6..33	20.43 ± 5.84	0.43
Matching to Sample	38.92 ± 12.41	36.45 ± 11.56	0.17

Table e-8. Baseline Automated Neurocognitive Assessment Metrics (ANAM) ***Subgroup comparisons of enlisted men only***			
ANAM module	mTBI (N=81) mean±SD	CTL (N=57) mean±SD	P value (Mann Whitney U)
Sleep index	2.16 ± 1.16	1.95 ± 0.97	0.35
Simple Reaction Time	247.16 ± 20.54	257.30 ± 55.65	0.46
Simple Reaction Time Repeat	256.93 ± 33.08	258.93 ± 40.23	0.74
Procedural Reaction Time	103.75 ± 12.76	103.61 ± 13.85	0.91
Code Substitution Learning	56.78 ± 11.86	56.67 ± 10.60	0.87
Code Substitution Delayed	50.00 ± 14.62	45.82 ± 16.43	0.16
Mathematical Processing	21.17 ± 6.40	19.56 ± 5.40	0.06
Matching to Sample	39.38 ± 12.48	35.40 ± 10.05	0.04*

*univariate statistical significance but not significant after correction for multiple comparisons.

Table e-9. Regions of Interest with significant FA group differences			
Region of Interest	FA mTBI (mean ± SD) N=95	FA CTL (mean ± SD) N=101	P Value (ANCOVA)
Superior Longitudinal Fasciculus Right	0.3933±0.0220	0.4050±0.0229	0.000057 *
Middle Cerebellar Peduncle Left	0.4119±0.0240	0.4222±0.0279	0.039
Superior Corona Radiata Right	0.3546±0.0237	0.3637±0.0228	0.023
Posterior Limb Internal Capsule Left	0.5284±0.0228	0.5354±0.0259	0.030
Superior Corona Radiata Left	0.3875±0.0232	0.3944±0.0224	0.042
Superior Longitudinal Fasciculus Left	0.4211±0.0184	0.4277±0.0226	0.046

FA Fractional Anisotropy; mTBI mild traumatic brain injury; CTL control

P values indicate univariate results for ANCOVA comparison between mTBI and control groups with age, gender and rank included as covariates.

*Statistically significant after false discovery rate correction for multiple comparisons across 56 regions of interest.

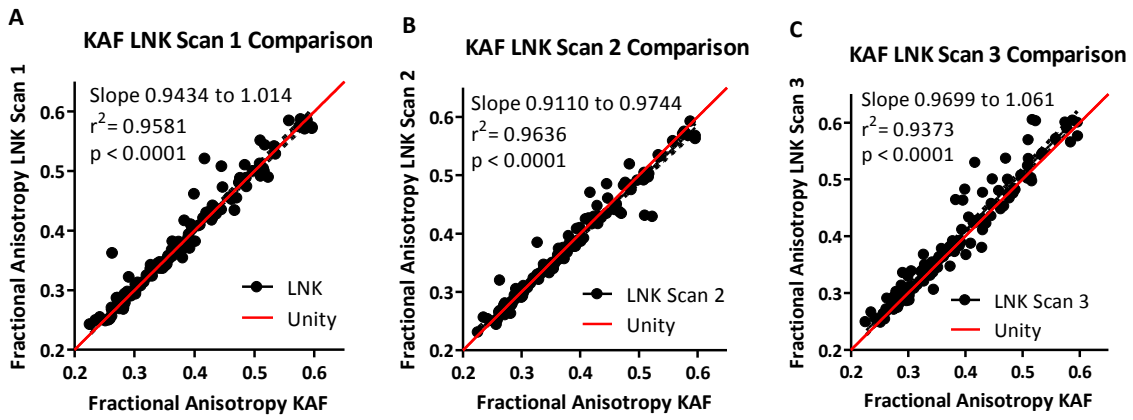

Figure e-1. Fractional Anisotropy Site Comparisons: Three MRI-DTI scans (A, B, C) acquired at LNK compared to a single scan acquired at KAF using the same healthy control show that FA comparisons are fairly centered on the line of unity, indicating no significant site effect on DTI acquisition across 56 regions of interest.

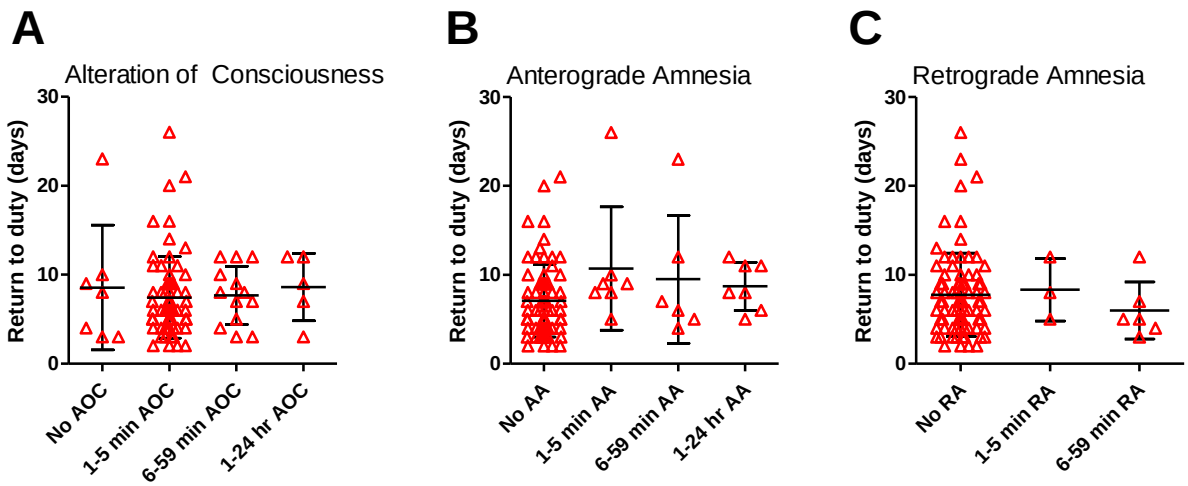

Figure e-2. No Relationship Between Return to Duty Time and Self-Reported Alteration of Consciousness or Amnesia. A. No relationship with alteration of consciousness (AOC). 1-way ANOVA $F(3,88)=0.21$, $p=0.89$. **B.** No relationship with anterograde amnesia (AA: for events after the injury). 1-way ANOVA $F(3,87)=1.9$, $p=0.13$. Data was not available for 1 subject. No relationship with retrograde amnesia (RA: for events before the injury). 1-way ANOVA $F(2,88)=0.44$, $p=0.64$. Bars shown indicate means and standard deviations.

SUPPLEMENTAL DISCUSSION There are several aspects of this study that warrant further discussion in relation to the previous literature and to inform future investigations.

Subject Characteristics

The exact mechanism of injury is difficult to ascertain in a chaotic combat environment. Thus, we cannot determine with certainty whether the subjects in the study sustained blast only or blast+impact TBI. Nonetheless, 42 mTBI participants reported a pure blast injury, 53 reported an associated head impact (e.g. motor vehicle rollover, being struck or striking an object) and 22 could not recall a possible compounding mechanism. A total of 40 mTBI participants sustained dismounted blast exposures (e.g. on foot patrol) while 55 were mounted (inside a tactical vehicle).

Additional Limitations

Level of education, which may impact performance on neurocognitive testing and vulnerability to mood disorders following TBI, was not collected in our study. The effects of age and gender on ANAM performance are well documented[13] while the influence of education is less well studied. Although SRT and PRT reflect reaction time with little cognitive processing, other ANAM cognitive modules may be more heavily influenced by education level. In order to account for this potential demographic confounder, we used individualized ANAM baselines as opposed to reference group normative data and replicated the results by conducting demographically matched subgroup comparisons using only enlisted men. The effect of education on ANAM performance appears to be minimal once age is controlled[9].

The injured cohort may not be representative of the combat mTBI service members at large because recruitment was restricted to the two highest level medical treatment facilities in

Afghanistan. However, the demographic characteristics are similar to those of other studies of combat mTBI[14, 15]. The mean recovery time is comparable to those reported by other concussion care centers in Afghanistan[16] (O Adam, D Rivet; unpublished data). The majority of mTBI patients treated at KAF and LNK were transported directly from point of injury, and therefore comparable to the patient population of other concussion care centers in Afghanistan. The most refractory mTBI patients referred from lower level concussion care centers in Afghanistan would not have been eligible for this study based on the time lapsed from their injury of over 7 days.

The collection of accurate data regarding loss or alteration of consciousness and PTA presents challenges when head injuries occur in a chaotic combat environment, impacting data reliability. Efforts were made to minimize such recall and documentation errors. The information was extracted directly from participants within days from injury by study staff experienced in the evaluation of mTBI, corroborated by third party accounts (combat medics or fellow service members present at the site of injury) and verified using combat records whenever possible.

Our conventional MRI protocol included GRE. The more sensitive susceptibility weighted imaging has gradually become the norm in clinical MR imaging in mTBI. However, data file sizes too large for transfers out of Afghanistan and scan duration were the main limiting factors taken into consideration in the decision to favor one blood-sensitive sequence over the other.

Another limitation is that we did not formally assess inter-rater reliability for the imaging analyses. The largely automated DTI Studio-based method was found to be very reliable in our unpublished assessments.

<u>Relationship to Previous Imaging Studies</u>

Neuroimaging has long played an important role in TBI. Computer tomography (CT) is widely available, including at combat hospitals in Afghanistan, and has short scan times. While it is very useful in screening out more severe head injuries that require medical evacuation and possible neurosurgical intervention, it is of limited utility in mTBI. Magnetic Resonance Imaging (MRI) is less widely available and involves longer scan times. In civilian settings, conventional brain MRI in the acute and subacute stages of mTBI can detect infrequent but clinically pertinent abnormalities with prognostic significance such as brain contusions and hemorrhagic axonal injury[17]. However, our findings are in line with numerous other studies of normal conventional MR imaging in mTBI[18], suggesting its limited clinical utility in this mildly injured patient population.

Previous studies[19,20] found differences in fractional anisotropy in additional brain regions in medically evacuated service members with mTBI. These findings were not replicated in our study population. In a previous military study performed at LRMC[19], 18/63 injured participants were found to have abnormal diffusion anisotropy (defined as two or more regions affected) on a single subject basis. In contrast, none of the subjects in this study could be determined unambiguously to have been injured based on DTI. These differences are likely attributable to dissimilarities in mTBI injury severity and possibly timing of imaging. The LRMC cohort consisted entirely of service members injured severely enough to be medically evacuated out of combat, whereas the subjects in this study had a 97% return to duty rate. Furthermore, the LRMC subjects were imaged within a median time of 14 days post-injury (range of one to 90 days), whereas in this study the median time to imaging from injury was 4 days. Animal studies and theoretical considerations indicated that DTI should be similarly sensitive at a range of acute time points[21, 22] but this has not been definitively established in human mTBI patients. While

both studies used similar imaging protocols (MRI 1.5T, isometric voxel sizes of 2.5mm), other notable differences such as scanner manufacturer and stability (the Avanto scanners used at LRMC may have had greater stability than the Achieva scanners in mobile trailers employed in this study) and number of diffusion directions may also account for differences in findings between these studies. In addition, region of interest selection was conducted differently in the two studies. In the LRMC study, a pre-specified 3D region of interest approach was used, as a whole brain DTI atlas was not available at the time. For this current cohort, we used a whole brain parcellation atlas to systematically sample regions throughout the entire brain anatomy. Some abnormalities may have been missed in the LRMC study due to the more limited region selection method that was employed."

Relationship to Previous Clinical Studies

There is a paucity of studies examining symptoms systematically and prospectively across multiple domains (somatic, cognitive, behavioral) in the acute stages of combat mTBI. In our study, the mTBI participants reported significantly more severe concussive symptoms, primarily somatic symptoms including headache, sensitivity to noise and dizziness. These results are consistent with prior findings of the most frequently endorsed symptoms acutely after injury of headache, dizziness, tinnitus and auditory symptoms[15, 23]. The frequency of LOC and alteration of consciousness in our cohort was higher than prior studies[15, 23] likely explained by dissimilarities in the study cohorts as well as methodology. LOC, alteration of consciousness and PTA are the most commonly used symptoms in the diagnosis and grading of mTBI[24-26]. They are also used by the Department of Defense in determining eligibility of service members for military awards such as Purple Heart. However, controversy exists regarding their reliability as predictors of recovery or future post-concussive syndrome (PCS) and disability. Our findings,

contrary to other studies of mTBI in military veterans of wars in Iraq and Afghanistan[23, 27], found no or weak correlations between loss or alteration of consciousness and recovery time. In sports mTBI, a greater number and severity of symptoms acutely after trauma are predictors of a prolonged recovery[28]. In our study, the total RPCSQ score correlated best with recovery time. This correlation may be construed to be the result of circular logic considering that the decision of return to duty was based on patient symptom reporting. However, the return to duty decision was based not on the initial RPCSQ score, but on symptom resolution, independent of initial symptom severity. A quantitative approach to symptom recording using standardized symptom inventories in the acute stages of combat mTBI may help predict recovery in blast-related mTBI. Traditional measures of loss or alteration of consciousness and amnesia, while used as clinical criteria for the diagnosis of mTBI, may not be sufficient for addressing mTBI severity, as they appear to correlate only modestly with duration of recovery. Clinical symptom resolution at rest and with exertion is currently used as the basis for return to duty determinations.

When somatic, cognitive and behavioral symptoms were tested together using a general symptom inventory (RPCSQ), behavioral symptom group comparisons recorded smaller effect sizes relative to somatic and cognitive symptoms acutely following the injury. A heightened perception of somatic relative to behavioral symptoms is consistent with findings of prior studies[23, 27]. When behavioral symptoms were assessed independently on measures of acute stress disorder/PTSD and depression/anxiety, group differences were sizable and significant. Unaccounted premorbid group differences in the level of combat intensity, prior history of unreported mTBIs and undiagnosed or unreported preexisting mental health conditions may have been contributors. However, an independent effect of mTBI cannot be excluded. There is a rapidly growing body of evidence supporting a strong association between combat mTBI and

subsequent development of mental health symptoms, including PTSD, depression and high combat stress in veterans of the conflicts in Iraq and Afghanistan[23, 29]. Even when accounting for other factors, such as a predeployment history of TBI, PTSD and combat intensity, TBI suffered during a most recent deployment remains the strongest predictor for post-deployment PTSD symptoms[30]. However, not all mTBI patients develop PTSD and it is unclear which specific early aspects of mTBI contribute to this increased risk. In our study, the PCLM and to a lesser extent the BDI correlated with recovery time. Quantitative behavioral assessments such as the PCLM performed in the acute stages of mTBI, might prove valuable tools for better stratifying these patients early for risk of future PTSD.

The use of standardized questionnaires such as the PCLM and BDI in the acute phase is not meant to establish a clinical diagnosis of PTSD or depression but to identify injured service members at risk. Such diagnoses are based on specific clinical criteria and a pre-determined duration of symptoms, which are not expected to be met by individuals without pre-morbid psychiatric history in the immediate stages after mTBI.

The PCL has been validated against structured clinical instruments[31-33] and it is widely used for PTSD clinical screening and research. In our study, the PCLM mean in the mTBI group, although significantly higher than in the control group, fell well below cut-point values (>40) considered to have the best sensitivity/specificity balance for PTSD diagnosis[31, 32, 34].

The mean BDI score, although significantly higher in the mTBI group compared to controls, also fell well below the cut-point score of 19 recommended for major depressive disorder screening in mTBI patients[5].

These findings suggest that lower PCLM and BDI cut-point values than those used for PTSD and depression screening may be clinically meaningful in the acute context of mTBI not

as diagnostic tools but as predictive markers for mTBI recovery, considering their correlation with recovery time.

Cognitive deterioration compared to individual baselines acutely following trauma are in line with prior studies of computerized neurocognitive assessment validity in mTBI screening in the first week after injury[14, 16, 27]. The largest effect size was demonstrated for SRT, which also correlated with mTBI recovery time, lending support to findings of prior studies that found SRT to be a sensitive tool for mTBI screening and recovery tracking[16, 27, 35]. Computerized neurocognitive assessment tools, specifically tasks that measure or incorporate reaction time, appear to be valuable tools that can be used by clinicians to predict recovery acutely in mTBI patients.

Despite significant group differences, overlap between healthy control and mTBI individual scores on clinical and neurocognitive testing underscores the non-specific nature of post-concussive symptoms. Better methods including advanced imaging and biomarkers for detecting mTBI and tracking recovery are needed.

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